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Original Article

Left ventricular function and myocardial perfusion before and after cardiac resynchronization therapy in chronic right ventricular apical pacing by echocardiogram-gated myocardial perfusion single photon emission computed tomography

Yuki Honda, MD*, Yuukei Higashi, MD, PhD, Mio Ebato, MD, PhD, Daisuke Wakatsuki, MD, PhD, Hisa Shimojima, MD, PhD, Hiroshi Suzuki, MD, PhD, Youichi Takeyama, MD, PhD

Division of Cardiology, Department of Internal Medicine, Showa University Fujigaoka Hospital, 1-30 Fujigaoka, Aoba-ku, Yokohama 227-8501, Japan

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ABSTRACT

Introduction: The aim of this study was to evaluate the changes in cardiac performance and myocardial blood perfusion by single photon emission computed tomography (SPECT) in patients upgrading to cardiac resynchronization therapy (CRT) from right ventricular apical pacing (RVAP).
Methods: Eleven patients (age, 70 ± 7.7 years; pacing career, 95 ± 48.8 months) with chronic RVAP were studied. Their baseline characteristics included New York Heart Association (NYHA) class ≥ 2, with left ventricular end-diastolic volume (LVEDV) > 55 mm or left ventricular ejection fraction (LVEF) < 50%, as shown by echocardiography. Cardiac function and cardiac blood perfusion of 17 segments were evaluated by SPECT. Cardio-GRAF (cardio Gated single photon emission computed tomography Regional Assessment for left ventricular Function), a left ventricular (LV) segmental time–volume analyzing program for SPECT, was used to assess dyssynchrony.
Results: Upgrading from RVAP to CRT resulted in an increase in LVEF and a decrease in LVEDV. The standard deviation of the time from the onset of QRS to end-systole in the 17 LV segments, which indicates LV dyssynchrony, showed the tendency to shorten from 98 to 70 ms. Furthermore, the %uptake of blood perfusion was increased at the inferoseptal lesion.
Conclusion: Upgrading to CRT from RVAP improved cardiac function and increased %uptake of blood perfusion at the inferoseptal lesion, as demonstrated by SPECT.

1. Introduction

Permanent right ventricular apical pacing (RVAP) is a standard treatment for patients with severe bradyarrhythmias; however, it alters the normal sequence of ventricular activation and can potentially increase the risk of heart failure and cardiac death [1]. RVAP alters the conduction of the heart in a manner that is similar to a left bundle branch block pattern, and hypoperfusion at the pacing site has been reported in clinical and experimental data [2,3]. RVAP leads to a delayed activation of lateral segments, resulting in intra- and interventricular dyssynchrony. Therefore, upgrading from RVAP to cardiac resynchronization therapy (CRT) in patients with long-term RVAP would be a reasonable approach for correcting dyssynchrony. CRT has been reported to improve hemodynamic function, heart failure symptoms, exercise capacity, and it also reduces morbidity and mortality [4].

Echocardiogram (ECG)-gated single photon emission tomography (SPECT) myocardial perfusion imaging represents an alternative tool for assessing cardiac function, as a novel program called cardioGRAF (cardio Gated single photon emission computed tomography Regional Assessment for left ventricular Function) enables the evaluation of regional left ventricular (LV) function, and can also detect mechanical dyssynchrony. The present study was a non-randomized, retrospective study to assess the dyssynchrony and myocardial blood perfusion changes after upgrading to CRT by SPECT, and to delineate the processes by which upgrading to CRT improves cardiac function.

2. Methods

2.1. Patient characteristics

Eleven patients with long-term chronic RVAP were studied (age 70 ± 7.7 years; Table 1). Their New York Heart Association (NYHA) scores were ≥ 2, with left ventricular diastolic diameters

* Corresponding author. Tel.: +81 45 971 1151; fax: +81 45 973 1019.
E-mail address: yukihonda333@gmail.com (Y. Honda).

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Table 1
Patient characteristics.

Age (years)	70 ± 7.7
Sex, M/F	7/4
Cause, ischemic/nonischemic	3/8
Pacing history (month)	95.0 ± 48.8
Cumulative % ventricular pacing	99.4 ± 0.5
NYHA class, 2/3/4	4/7/0
Plasma BNP level (pg/mL)	390 ± 575
QRS duration (ms)	193 ± 35
EF (%)	45.6 ± 9.5
LVEDV (mL)	149.7 ± 37.9
LVESV (mL)	83.5 ± 28.5

over 55 mm or left ventricular ejection fractions (LVEF) below 50%, as demonstrated by echocardiography. A permanent pacemaker was implanted in 11 patients in the atrioventricular block, and in 4 patients with sick sinus syndrome and atrial fibrillation with a slow ventricular response. All pacing leads were located at the right ventricular apical region. The patients' underlying heart diseases included valvular disease (3 patients), ischemic heart disease (2 patients), hypertensive heart disease (1 patient), and idiopathic disease (4 patients). One patient's underlying heart disease was unknown (myocarditis was suspected). Both of the ischemic heart disease patients had a history of anterior myocardial infarction, and perfusion defects at the left descending artery area were observed before pacemaker implantation. The duration of RVAP was 95 ± 48.8 months, and the cumulative ventricular pacing was $99.4 \pm 0.5\%$. All patients received optimal medical therapy for heart failure; specifically, 57% of the patients were taking angiotensin converting enzyme inhibitors or angiotensin–receptor blockers, 71% were taking beta-blockers, 86% received diuretics, 14% were taking amiodarone, and 43% of the patients received digoxin.

2.2. Biventricular pacemaker implantation

Implantation of biventricular pacemakers was performed by following established protocols. Retrograde venous angiography was performed through a subclavian venous access to confirm the coronary sinus branch. The LV lead was implanted in the lateral or posterolateral mid-ventricular region of the LV.

2.3. SPECT imaging and analysis

After the injection of 740 MBq of ^{99m}Tc-sestamibi while at rest, the SPECT images were acquired by a dual-headed angular rotating gamma-camera system (Vertex; ADAC Laboratories, Milpitas, CA, USA) equipped with a low energy general purpose collimator (30 projections during an 180° rotation, 16-frame gating, and 128×128 matrices) for long-term RVAP patients prior to CRT upgrading. Cardiac function and volume was assessed with SPECT before upgrading to CRT (3 ± 2.7 months before upgrading). Ejection fraction (EF) was derived from the left ventricular cavity volumes of the end diastolic volume (EDV) at end-diastole and the end systolic volume (ESV) at end-systole as follows: $\%EF = (EDV - ESV)/EDV \times 100$. The modeling procedure provided parametric polar maps of cardiac blood perfusion (%uptake) in 17 segments. Each of the counts on the polar map was normalized to the highest count, which was assigned a value of 100%. Segments outside of the field of view of the SPECT scanner were excluded. As a follow-up, the SPECT analyses were performed according to the same protocol 16.4 ± 13.1 months after upgrading to CRT.

2.4. CardioGRAF analysis

The images were processed with pFAST (perfusion and function assessment by means of gated SPECT) version 2.4 to determine the inner LV edge. The pFAST data files were further processed with cardioGRAF (cardio Gated single photon emission computed tomography Regional Assessment for left ventricular Function; FUJIFILM RI Pharma Co., Ltd., Tokyo, Japan) to generate the global and regional time–volume curves; these curves represented the 17 LV segments that were divided according to the recommendation of the American Heart Association Scientific Statements [5].

2.5. Statistical analysis

Data are given as mean value $\pm$ 1 standard deviation (SD). The student's *t*-test for unpaired groups was used to compare cardiac blood perfusion (%uptake). Probability values were calculated by using 2-sided tests and $p < 0.05$ was considered statistically significant.

3. Results

After upgrading to CRT, the QRS duration shortened significantly (193 ± 35 ms vs. 134 ± 23 ms, $p < 0.01$) and the plasma brain natriuretic peptide (BNP) level showed a tendency to decrease (390 ± 575 pg/mL vs. 132 ± 99 pg/mL, p=NS). LVEF increased significantly ($45.6 \pm 9.5\%$ vs. $54.6 \pm 7.2\%$, $p < 0.01$), and left ventricular end-diastolic volume (LVEDV) and left ventricular end-systolic volume (LVESV) decreased significantly (149.7 ± 37.9 mL vs. 134.4 ± 42.0 mL, 83.5 ± 28.5 mL vs. 62.5 ± 27.8 mL, respectively, $p < 0.05$; Fig. 1). The standard deviation of the time to end-systole from the onset of QRS complex in the 17 LV segments, which indicates LV dyssynchrony, had a tendency to shorten from 98 to 70 ms (p=NS; Fig. 2) Furthermore, the %uptake of blood perfusion of at the inferoseptal region increased significantly and the %uptake at the contrary lateral free wall region was significantly decreased with CRT (segment 2: $38 \pm 8\%$ vs. $47 \pm 10\%$, $p < 0.05$, segment 9: $69 \pm 12\%$ vs. $81 \pm 4\%$, $p < 0.01$, segment 10: $66 \pm 10\%$ vs. $75 \pm 7\%$, $p < 0.05$, segment 12: $89 \pm 5\%$ vs. $84 \pm 5\%$, $p < 0.05$; Fig. 3).

4. Discussion

This study demonstrated that upgrading to CRT from RVAP improved cardiac performance and myocardial perfusion at pacing sites by SPECT. RVAP has been reported to alter left ventricular electrical and mechanical activation in a manner that is similar to the complete left bundle branch block pattern [2]. In a study utilizing SPECT, RVAP was associated with a high incidence of perfusion defects in the absence of coronary artery disease [6]. To add to the knowledge of the relationship between RVAP and coronary blood flow, Skalidis et al. reported that a significant reduction of flow velocity was observed in the epicardial coronary artery at pacing sites [2]. Furthermore, an experimental study in a canine model by Carew et al. demonstrated that the difference between the perfusion pressure in the artery and the intramyocardial pressure determined the fractional systolic and diastolic flow in the myocardial wall [7]. Another canine study by Ono et al. revealed that the diastolic–intramyocardial pressure in the septum increased significantly after induction of RVAP [8]. In general, the flow in the epicardial coronary artery shows a phasic pattern, and a large amount of flow occurs in the diastolic period. Transmural compression of the intramyocardial vessels during systole and the release of the compression force

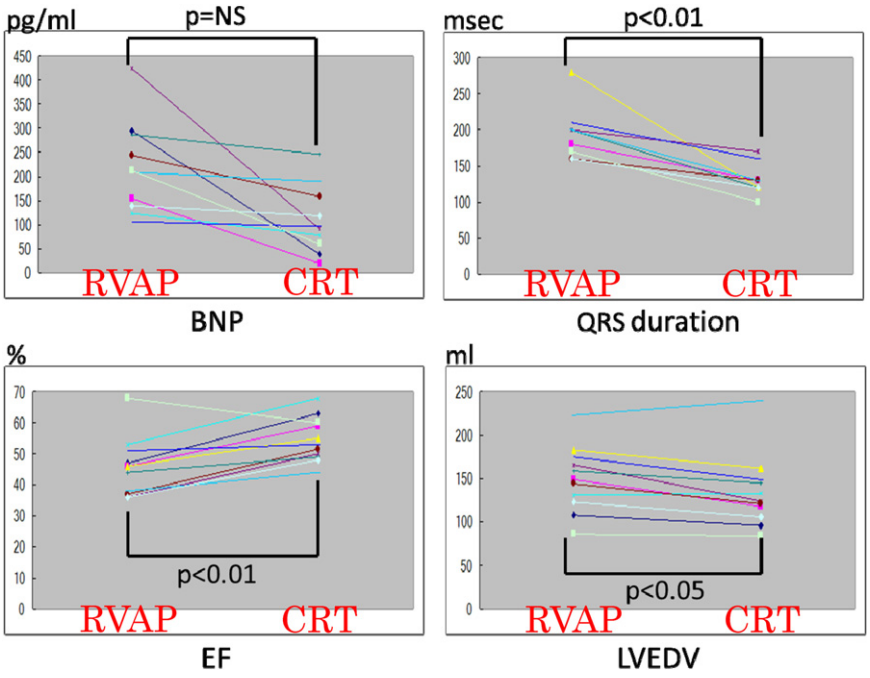

Fig. 1. Alterations in plasma BNP level, QRS duration, EF, and LVEDV before and after CRT.

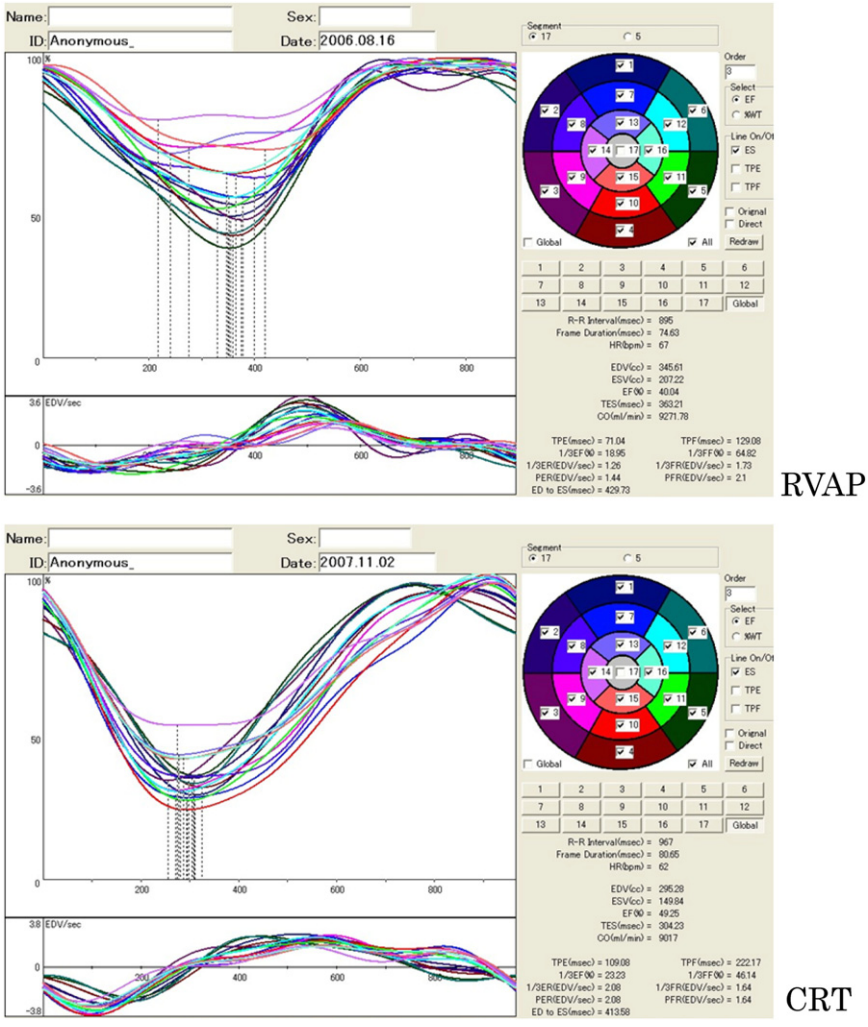

Fig. 2. Correction of LV dyssynchrony after upgrading to CRT in 17 LV segments. The changes in the standard deviation of the time from the onset of QRS to peak-systole in 17 LV segments had the tendency to shorten from 98 to 70 ms after upgrading to CRT.

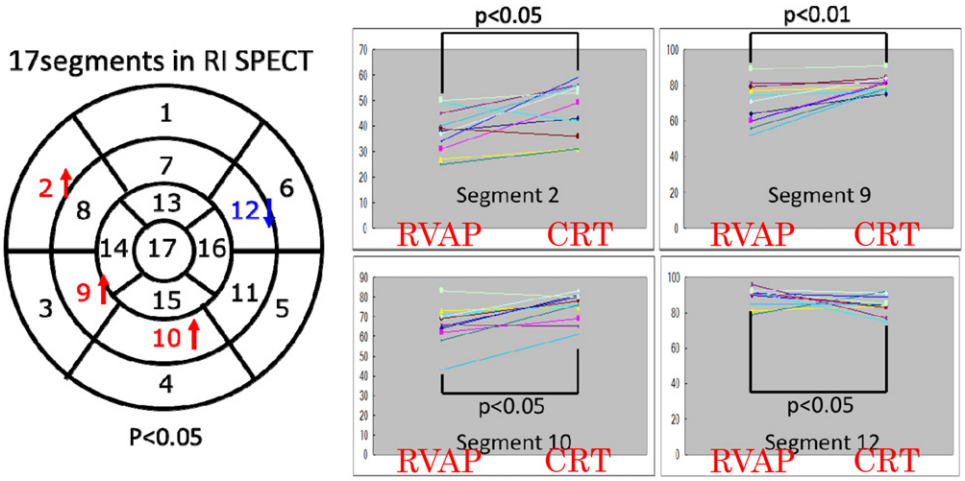

Fig. 3. Changes in %uptake of blood perfusion of 17 LV segments by RI SPECT before and after upgrading to CRT. The %uptake of blood perfusion increased at the inferoseptal region (segment 9 and 10), and decreased at the contrary lateral region (segment 12).

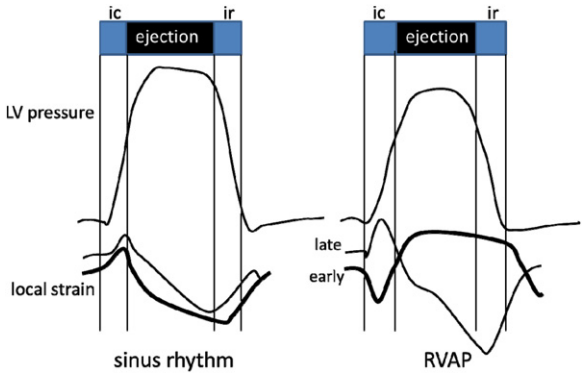

Fig. 4. Effect of asynchronous ventricular activation. The upper and lower tracings indicate LV pressure and local strain, respectively. In RVAP, higher strain is prolonged in the early excitation region compared with the sinus rhythm, which may lead to increasing intramyocardial pressure of the pacing sites during the early diastolic period.

during diastole cause this pattern [9]. These studies suggested that the increased septal intramyocardial pressure during the diastolic phase of the RVAP, when originally intended to decrease the intramyocardial pressure in normal electrical and mechanical sequence, led to coronary vessel resistance, thereby resulting in the reduced coronary blood flow and myocardial perfusion in the pacing sites.

Although it is unclear why the septal intramyocardial pressure increases during the diastolic period while on RVAP, considering that RVAP causes an increase in QRS duration similar to a left bundle branch block pattern, this observation may be due to electrical and mechanical changes induced by RVAP. It is generally understood that RVAP induces early contraction of regions that are close to the pacing site, which stretch the remote regions that are not yet activated. This stretching further delays the shortening of these late-activating regions and increases their force of local contraction, by virtue of the Frank–Starling mechanism. Consequently, the late-activating regions impose loading on the earlier activated pacing territories, a phenomenon known as "systolic paradoxical stretch". This non-physiological force that occurs in the diastolic period may cause increases in intramyocardial pressure that lead to reduction of the blood perfusion in the pacing site (Fig. 4). In this study, all cases of QRS duration shortened significantly, and the standard deviation of the time from the onset of QRS to end-systole in the 17 LV segments that indicate LV dyssynchrony tended to improve; furthermore, the cardiac perfusion increased at the inferoseptal region and decreased at the contrary free wall region, after upgrading to CRT. Particularly, the cardiac perfusion of segment 9 in SPECT located at the pacing lead increased in all cases. These results indicated that CRT could mechanically and electrically correct the dyssynchrony associated with RVAP, resulting in reduction in intramyocardial pressure and an increase in cardiac blood perfusion in the pacing sites. In short, CRT could restore the cardiac perfusion that was unbalanced by RVAP.

While it was unclear as to why no significant difference was observed in the standard deviation of the time from the onset of QRS to end-systole in the 17 LV segments by radio isotope (RI)-SPECT, this lack of statistical significance might be due to the small number of the patients in this study, the varying locations of the RV lead position, and patient variability with respect to the degree of intrinsic conduction abnormality.

An experimental MRI study in dogs showed that systolic fiber strain and external work were almost 0 at the pacing site, and more than twice that in the right atrial pacing in the contrary remote regions [10]. With echocardiography, LV wall systolic thickening at the pacing lesion is not obvious [11]. Furthermore, another study demonstrated that blood flow varied in parallel with regional function during ventricular pacing [12]. Taking these findings into consideration, RVAP would reduce the cardiac blood flow in pacing sites by increasing the intramyocardial pressure, which would impair cardiac function, this would result in increased left ventricular pressure and increased intramyocardial pressure by stretching the cardiac muscle, thereby establishing a "vicious cycle". The current study, while including mild heart failure patients compared with the guidelines for CRT implantation, demonstrated that CRT could remodel the left ventricle with RVAP. This procedure will result in the redistribution of cardiac blood perfusion to the LV.

5. Study limitations

Our study consisted of a small number of cases, and the results of this procedure should be evaluated in larger number of patients. Our study subjects had better overall cardiac function than patients for whom implant CRT is usually recommended, according to American Heart Association/American College of Cardiology/Heart Rhythm Society guidelines. Although CRT with RVAP could improve cardiac function even in the comparatively

functionally preserved heart, this fact might have affected our results.

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